

REMARKS

I. Amendments

By this amendment, claims 1-4, 10-13, 20 and 26-29 have been amended, and claims 5, 21-25 and 30-33 have been cancelled.

Support for the amendment to claim 20 to recite carriers may be found at page 117, line 11 – page 120, line 22 *inter alia*.

No change of inventorship is necessitated by this amendment.

In addition, minor spelling, typographical and grammatical errors have been corrected by this amendment.

A parentage statement with an indication of priority has also been added to the specification.

II. Discussion of the Restriction Requirement

Applicants hereby confirm their previous election to prosecute the aspects of the invention set forth in the claims of Group I (claims 1-33). By this amendment, the claims have been amended to limit them to compounds wherein A is a 5-membered nitrogen-containing heterocyclic ring. Applicants submit that the claims as amended are now in conformance with the restriction requirement.

III. Discussion of the Rejection for Improper Markush Groups

By this amendment, the claims have been amended to limit them to compounds wherein A is a 5-membered nitrogen-containing heterocyclic ring as stated in Sec. II above. Applicants submit that the claims as amended are drawn to proper Markush groups, and respectfully request withdrawal of the rejection.

IV. Discussion of the Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement accompanies this response. The Statement includes the references cited in the International Search Report. A copy of the ISR was filed on February 13, 2002. Yet the Examiner did not mention the review of these references in the Office Action, so they are now being submitted in the form of an IDS along with additional references for consideration. The Examiner's consideration of the references is requested.

V. Discussion of the 35 U.S.C. Sec. 112, First Paragraph Rejection of Claims 18 and 20-33

Claims 18 and 20-33 have been rejected under 35 U.S.C. Sec. 112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse this rejection.

Claims 18 and 20-33 have been rejected for the use of the term "prodrug". Applicants disagree that the specification provides no guidance. In fact, in the specification, prodrugs are defined on page 114, line 21 – page 116, line 7. Applicants believe that the specification provides enough detail for one skilled in the art of synthesis to understand the invention.

By this amendment, claims 21-25 and 30-33 have been cancelled, thereby rendering the rejection as to those claims moot.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, first paragraph rejection.

VI. Discussion of the 35 U.S.C. Sec. 112, First Paragraph Rejection of Claims 23-33

Claims 23-33 have been rejected under 35 U.S.C. Sec. 112, first paragraph as allegedly lacking enablement. Applicants respectfully traverse this rejection.

Claims 23-33 have been rejected for the use of the phrase "preventing or".

As an initial matter, Applicants note that claims 29 and 33 do not contain the phrase “preventing or”.

By this amendment, the phrase “preventing or” has been deleted from the claims 26 and 27. The phrase has been retained in claim 28, as Applicants believe that restenosis can be prevented with the compounds as recited in pending claim 28.

The Examiner has also indicated that the method claims lack enablement for treatment of various diseases based on the examples which demonstrate inhibition of lipid peroxidation in the specification. Applicants disagree.

The Specification Teaches Methods of Treating with Compounds of the Present Invention

For the methods of treating certain diseases and conditions recited in claims 26-28, Applicants believe these claims are adequately supported by the specification as well. Lipid peroxidation inhibitors can be useful to treat the recited diseases and conditions, as is understood by those skilled in the art. On page 5, line 11 – page 6, line 18 of the specification the relationship of lipid peroxidation inhibition to the recited diseases and conditions is discussed.

The specification also provides evidence that compounds of the present invention are lipid peroxidation inhibitors. Applicants have shown that representative compounds of the present invention are useful for the inhibition of lipid peroxidation in the Test Example on page 168, line 22 – page 170, line 6 of the specification.

Applicants contend that one skilled in the art would understand how to practice the invention, given the teachings of the specification and the state of the art; as the connection between lipid peroxidation inhibition and treatment of certain conditions is known. The scientific literature illustrates what is known about the connection, as explained in the following paragraphs.

Scientific Literature Illustrates the Relationship Between Inhibition of Lipid Peroxidation Inhibition and Certain Conditions

To illustrate that one skilled in the art would understand the relationship between a demonstrated capability to inhibit lipid peroxidation, and treatment of the claimed conditions, Applicants have provided literature references in attached Appendix A. Each literature reference will be discussed separately, in light of the claim for which it has been provided to support.

Literature Support for Claim 26- Delanty *et al.*

In claim 26 as amended, a method for treating cerebrovascular impairment, cranial trauma or neurodegenerative disease with compounds of the present invention is recited. Delanty *et al.* (Acta Neurol. Scand., vol. 98, pp. 145-153, 1998) summarizes trials which tested whether certain antioxidants were useful in combating disease.

Since increased lipid peroxidation is a factor in neurodegenerative diseases such as Alzheimer's, antioxidants which inhibit lipid peroxidation may be effective, according to the article. On page 148 of Delanty *et al.*, vitamin E is described as useful for Alzheimer's disease. Applicants therefore believe that one skilled in the art would understand the utility of compounds of the present invention for treatment of neurodegenerative disease.

On page 150, a study of tirilazad is described wherein acute spinal cord injury efficacy was studied. Tirilazad, a lipid peroxidation inhibitor, was shown to be effective. The article also states that lipid peroxidation is involved when there is traumatic injury to the nervous system. Applicants therefore believe that one skilled in the art would understand the utility of compounds of the present invention for treatment of cranial trauma.

Tests to ascertain the utility of lipid peroxidation of inhibitors for the treatment of cerebrovascular disease are described on pages 147 and 148 of Delanty *et al.* Vitamin E intake was shown to correlate inversely with carotid plaque thickness. Applicants therefore believe that one skilled in the art would understand the utility of compounds of the present invention for the treatment of cerebrovascular impairment.

Literature Support for Claim 27 – Parekh *et al.*

In claim 27 as amended, a method for treating dysuria or urinary incontinence with compounds of the present invention is recited. Applicants have shown that representative compounds of the present invention are useful for the inhibition of lipid peroxidation in the Test Example on page 168, line 22 – page 170, line 6 of the specification.

On page 1, line 20 of the specification it is indicated that derivatives of natural antioxidants such as vitamin E are used as lipid peroxide inhibitory agents.

In Parekh *et al.* (The Journal of Urology, Vol. 166, pp. 341-346, 2001) on page 341, it is explained that lipid peroxidation indirectly results in membrane damage, wherein membrane damage underlies bladder dysfunction. Experiments showed that when a partial outlet

obstruction was created in rabbits and a diet supplemented with vitamin E was fed to some of the rabbits with obstructions, that those rabbits on a supplemented diet experienced beneficial effects on their bladder functioning as stated on page 343.

This literature reference indicates that lipid peroxidation inhibitory agents (herein vitamin E) can improve bladder function. Given this reference, one skilled in the art could find that such a lipid peroxidation inhibitory agent would be useful for treating urinary tract diseases or disorders such as the claimed dysuria and urinary incontinence.

Literature Support for Claim 28 – Jeremy *et al.*

In claim 28 as amended, methods for preventing or treating restenosis with compounds of the present invention are recited. The literature reference of Jeremy *et al.* (J. Card. Surg., vol. 17, pp. 324-327, 2002) is provided to support this claim.

In Jeremy *et al.*, superoxide is indicated to be a key risk factor for cardiovascular disease, including restenosis. The relationship of superoxide to lipid peroxidation is also described; that superoxide promotes deleterious lipid peroxidation. One skilled in the art would understand how lipid peroxidation inhibitors (antioxidants) could combat the effects of superoxide and thus play a role in treating cardiovascular disease. Moreover, the article indicates that antioxidants reduce vasculopathy on page 325. Applicants therefore believe that one skilled in the art would understand the utility of compounds of the present invention for the treatment of restenosis.

Applicants submit that given the state of the art (as indicated by submitted literature references) and the teachings of the specification the method claims are sufficiently enabled.

In addition, methods of administration of the compounds are discussed on page 117, line 11 – page 118, line 20.

By this amendment, claims 23-25 and 30-33 have been cancelled, thereby rendering the rejection as to those claims moot.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, first paragraph rejection.

VII. Discussion of the 35 U.S.C. Sec. 112, Second Paragraph Rejection

Claims 5, 7-13, 19-26 and 30-33 have been rejected under 35 U.S.C. Sec. 112, second paragraph as allegedly lacking a clear written description of the invention. Applicants respectfully traverse this rejection. Several objections have been made, so each will be discussed separately in the following paragraphs.

Objection (a) to Claim 5

In the first aspect of the rejection, claim 5 was objected to. By this amendment, claim 5 has been deleted due to the restriction requirement, so Applicants submit that this aspect of the rejection is moot.

Objection (b) to claims 7, 10 and 19

In the second aspect of the rejection, claims 7, 10 and 19 were objected to for inclusion of the phrase “other symbols”. Applicants believe that those skilled in the art understand what is meant by the phrase, that is the variables which are not specified in the claim but which are in the formula are as defined in the independent claim which they relate to. For example, in claim 7, definitions of R^4 and R^5 are recited, so the “other symbols” would be R, A and C. Applicants do not find the use of the phrase to be indefinite. Moreover, the Applicants have many issued patents wherein the phrase was utilized without it being termed indefinite. Examples are U.S. Patent No. 6,613,805 (claim 24); 6,326,369 (claim 14); and 6,417,213 (claim 20).

Also, in this case, Mukund Shah is listed as this Examiner’s supervisor. Mukund Shah is listed as the Examiner on some of Applicants’ patents wherein “other symbols” was found to be acceptable claim language. The Examiner is requested to consider U.S. Patent No. 5,403,843 (claim 35); 6,627,630 (claim 1) and 6,172,085 (claim 19) in this regard.

Therefore, Applicants submit that claims 7, 10 and 19 are not rendered vague by the recitation of “other symbols”.

Objection (c) to claims 11-13

The Examiner has indicated a lack of antecedent basis for “halogen atom, hydroxy” in claims 11-13. Applicants wish to thank the Examiner for pointing out this discrepancy. They

discovered an error in translation of their priority document, whereby halogen and hydroxy are not options for R², but rather optional further substituents of the R² lower alkyl group. Claims 11-13 have been amended accordingly. This amendment adds no new matter to the specification. Support for the amendment may be found at page 15, line 13- page 18, line 4 *inter alia*. In claim 10, R² can be an optionally substituted hydrocarbon group. On pages 15-18, substituents of hydrocarbon groups are listed. Hydroxy is option 26 and halogen is option 1. Applicants submit that this aspect of the rejection has been overcome.

Objection (d) to claims 20, 26 and 30

Claims 20, 26 and 30 have been objected to for the description of the substituent of ring A in the proviso.

By this amendment, the proviso has been deleted from claims 20 and 26, rendering the rejection moot.

By this amendment claim 30 has been cancelled.

Applicants submit that this aspect of the rejection has been overcome.

Objection (e) to claims 21 and 22

Claims 21 and 22 have been objected to as duplicate claims. By this amendment claims 21 and 22 have been cancelled, thereby rendering this aspect of the rejection moot.

Objection (f) to claims 23-25

Claims 23-25 have been objected to as vague in the recitation of "an agent". By this amendment, claims 23-25 have been cancelled.

Objection (g) to claims 30-33

Claims 30-33 have been objected to as allegedly indefinite use claims. By this amendment claims 30-33 have been cancelled, thereby rendering this aspect of the rejection moot.

By this amendment, claims 5, 21-25, and 30-33 have been cancelled, thereby rendering the rejection moot.

Therefore, Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 112, second paragraph rejection of claims 5, 7-13, 19-26 and 30-33.

VIII. Discussion of the Rejection of Claims 30-33 under 35 U.S.C. Sec. 101

Claims 30-33 have been rejected under 35 U.S.C. Sec. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process.

By this amendment, claims 30-33 have been cancelled, thereby rendering the rejection moot.

Therefore, Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 101, rejection of claims 30-33.

IX. Discussion of the Rejection under 35 U.S.C. Sec. 102(b) over Bhalerao *et al.*

Claims 1 and 19 have been rejected under 35 U.S.C. Sec. 102(b) as allegedly being anticipated by Bhalerao *et al.*, (Arzneim.-Forsch./Drug Res. 44 (II) Nr. 9 (1994)). Applicants respectfully traverse the rejection.

By this amendment, Applicants have amended claim 1 to recite the identity and substituents of ring A in greater detail. This amendment adds no new matter to the specification. Support for the amendment may be found at page 31, line 6 – page 34, line 20 *inter alia*.

Most particularly, Applicants would like to point out that ring A of the compounds of the present invention as set forth in independent claim 1 as amended is made of carbon and nitrogen atoms. In lines 10 and 11 of page 31 of the specification, it is stated that the ring “contains at least one nitrogen atom in addition to carbon atoms...”. Given this statement, one skilled in the art would understand that ring A is made up of carbon and nitrogen atoms. Thus an oxazoline ring is not an option for ring A, as in compound 2 in Table 1 of the cited reference.

The specific examples of ring A listed on page 31, lines 11- 14 do not include compounds having oxygen in their rings. These examples reinforce the understanding that oxygen is not a ring A atom. For this reason, the compounds of the present invention as set forth in claim 1 as amended are not anticipated by the cited reference.

Claim 19 depends upon claim 1. Applicants submit that the more specific dependent claim is also not anticipated by the cited reference for the reason given above.

Therefore, Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 102(b) rejection.

X. Discussion of the Rejection under 35 U.S.C. Sec. 103(a) over Ohkawa *et al.*

Claims 1-13, 19-22, 26 and 30 have been rejected under 35 U.S.C. Sec. 103(a) as being unpatentable over Ohkawa *et al.*, U.S. Patent No. 6,034,239. Applicants respectfully traverse the rejection.

By this amendment, Applicants have amended claim 1 to recite the identity and substituents of ring A in greater detail. This amendment adds no new matter to the specification. Support for the amendment may be found at page 31, line 6 – page 34, line 20 *inter alia*.

Most particularly, Applicants would like to point out that the specific substituents of ring A of the compounds of the present invention as set forth in independent claim 1 as amended do not include an equivalent of the Y substituent $-(CH_2)_m-N(R^2)-C(O)R^1$ on the right-hand ring of the cited reference.

For this reason, the compounds of the present invention as set forth in claim 1 as amended are not obvious in view of the cited reference.

Claims 2-4, 6-13, 19, 20 and 26 depend upon claim 1. Claims 5, 21, 22 and 30 have been cancelled. Applicants submit that the more specific dependent claims are also non-obvious for the reason provided above.

Therefore Applicants respectfully request withdrawal of the 35 U.S.C. Sec. 103(a) rejection over Ohkawa *et al.*

XI. Discussion of the Non-Statutory Double Patenting Rejection

Claims 1-13, 19-22, 26 and 30 have been rejected under the judicially-created doctrine of obviousness-type double patenting over claims 1-11, 15-20, 22-24 and 31-34 of U.S. Patent No. 6,034,239.

Applicants respectfully request that the Examiner reconsider this rejection in view of the amendments to the claims and the arguments made in Sec. X above with respect to this reference.

Applicants respectfully request withdrawal of the double patenting rejection.

XII. Discussion of the Objections to the Claims

Claim 10 has been objected to as a multiply dependent claim in improper form. By this amendment, claim 10 has been amended to be solely dependent upon claim 1.

The Examiner has indicated that claims 14-17 would be allowable if re-written in independent form. Applicants acknowledge this point, but respectfully request re-consideration and confirmation of the allowability of claims 14-17 in light of the Information Disclosure Statement which accompanies this response.

XIII. Conclusion

Reconsideration of the claims as amended and allowance is requested. Should the Examiner believe that a conference with Applicants' attorney would advance prosecution of this application, the Examiner is respectfully invited to call Applicants' attorney at the number below.

Respectfully submitted,

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